DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103948/0

MAY 0 7 2001

Michael A. Recupero
Millennium and ILEX Partners, LP
75 Sidney Street
Cambridge, MA 02139

Dear Mr. Recupero:

This letter hereby issues Department of Health and Human Services U.S. License No. 1289 to Millennium and ILEX Partners, LP, Cambridge, MA, in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Alemtuzumab. Alemtuzumab is indicated for the treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy.

Under this authorization, you are approved to manufacture Alemtuzumab at ———— In accordance with approved labeling, Alemtuzumab will be distributed by Berlex Laboratories in Richmond, CA under the tradename Campath and marketed in 30 mg (10 mg/mL) ampoules.

You are not currently required to submit samples of future lots of Alemtuzumab to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay prior to lot release and release of only those lots that meet specifications.

The dating period for Alemtuzumab shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. The dating period of the bulk drug substance shall be six months when stored at 2-8°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

Any changes in the manufacturing, testing, packaging or labeling of Alemtuzumab, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As requested in your letter of February 13, 2001, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe the clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Alemtuzumab, or are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of a clinical study, as outlined in your commitment of March 16, 2001:

1. We acknowledge your intention to address the commitment of verification of the clinical benefit of Alemtuzumab therapy by conducting protocol ——— "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) versus Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia", submitted on March 16, 2001, and revised on April 20, 2001. As described in your letters of April 12 and May7, 2001, completion of patient accrual will occur in June 2004, completion of the study will occur in February 2006, and the final study report including SAS datasets and applicable revised labeling will be submitted in November 2006. It is understood that, to fulfill the requirements of accelerated approval, the study must be conducted with due diligence and must demonstrate that Alemtuzumab provides superior disease-free survival, as compared to chlorambucil, with comparable or acceptable toxicity.

We acknowledge that you have committed to do the following as part of protocol ——— (using the schedule for completion described above) and results submitted with the final study report by November 2006:

2. Immunological assessment of the effect of Alemtuzumab therapy on responses to vaccinations for infectious diseases.

3. Assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following Alemtuzumab therapy.

4. A quantitative analysis of the incidence and magnitude of HAHA and anti-idiotypic antibodies at study entry and following exposure to Alemtuzumab.

We also acknowledge the additional written commitments of March 5, March 16, April 27, and May 3, 2001, which include the following:

5. Submission of the final study report for protocol ———— "A Phase II Study, Including Pharmacokinetics, of CAMPATH-1H in Patients with B-Cell Chronic Lymphocytic Leukemia Who Have Received Treatment with a Purine Analogue" in August 2001.

6. Submission of the validation plan for the human-anti-humanized antibodies (HAHA) assay in July 2001 and the validation report in September 2001.

7. Submission of the validation plan for the FACS based immune function assay in June 2001 and the validation report in September 2001.

8. To evaluate data from the CMCL potency assay (QA 10379) and the monomer content assay (QA 10371) performed for lot release of bulk drug substance and drug product over the year following approval (or the next ten lots) and to tighten the lot release specifications appropriately with submission of a manufacturing supplement by June 2002.

9. To evaluate data from the residual Protein A assay (QA 10370) performed for lot release of the bulk drug substance over the year following approval (or the next ten lots) and to tighten the lot release specifications appropriately with submission of a manufacturing supplement by June 2002.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, as specified in 21 CFR 601.45, any advertising and promotional labeling is required to be submitted using FDA Form 2567 or Form 2253 to the Advertising and Promotional Labeling Branch, HFM-602, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448 for review and approval at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotion labeling.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Steven A Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research